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09/755,205	01/04/2001	Xiangzhong Yang	UCON-150	4832

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EDWARDS & ANGELL  
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BOSTON, MA 02209

EXAMINER

AFREMOVA, VERA

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 09/04/2003

4

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/755,205

Applicant(s)

YANG ET AL.

Examiner

Vera Afremova

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on 27 June 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☐ Claim(s) 36-45 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) \_\_\_\_\_ is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)                      4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)                      5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 14.                      6) ☐ Other:

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/27/2003 has been entered.

#### ***Status of claims***

Claims 36-45 are pending and under examination.

Claims 1-35 are canceled by applicants [paper No. 16 filed 6/27/2003].

#### ***Claim Objections***

Claims 36-45 are objected to because of the following informalities:

Claims 36 and 40 indicate heat conductivity in units "W/(m-k)". It appears that the symbol "-" might be incorrect. It is believed that the thermal conductivity is measured in units "W/m K" or "W m<sup>-1</sup> K<sup>-1</sup>". Upon clarification the appropriate correction is required.

Claim 40 appears to contain some typing error in the phrase "raising" in the recitation of step b). It is believed to be "rinsing", for example: see original claims or see claim 40 as filed on 10/07/2002. Appropriate correction is required.

#### ***Claim Rejections - 35 USC § 112***

Claims 40-44 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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Claim 40 recites the limitation "said solid surface" in step b), for example: see last line of step b). There is insufficient antecedent basis for this limitation as claimed because there is no solid surfaces in preamble or in step a). In alternative, it is uncertain whether "said" solid surface of step b) is the same as "a solid surface" in step c). In the instant office action two solid surfaces are considered to be the same.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 36 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,780,295 [IDS filed 10/09/2001, reference #2].

Claims are directed to a method for cryopreserving biological material wherein the method comprises step of suspending the biological material in a vitrification solution and step of directly contacting droplets of the suspension of biological material in the vitrification solution with a solid surface wherein the surface has a thermal conductivity greater than 10 W/mK and a temperature of about -150°C to about -180°C, wherein the droplets have size of not exceeding 10 µL and wherein the vitrification solution has a concentration of cryoprotectant sufficient to prevent ice formation upon contacting with solid surface. Some claims are further drawn to the use of biological material such as cells in the method for cryopreserving the biological material.

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US 5,780,295 teaches a method for cryopreserving biological material wherein the method comprises step of suspending the biological material in a cryosolution or vitrification solution (col. 5, lines 29-39 and col. 13, lines 1-50) and step of directly contacting droplets of the suspension of biological material in the vitrification solution with a solid cryogenic surface (col. 5, lines 44-45) wherein the solid surface is a metal surface (col. 5, line 52; col. 7, line 8) which is precooled with a liquid cryogen to about  $-160^{\circ}\text{C}$  (col. 4, line 22), wherein the droplets have diameter 25-200  $\mu\text{m}$  which is the size not exceeding 10  $\mu\text{L}$  {for example: volume of a droplet with diameter of 25  $\mu\text{m}$  or radius (  $r$  ) of 12.5  $\mu\text{m}$  would be  $8.2 \times 10^{-6} \mu\text{L}$  accordingly  $v = \frac{4}{3} \pi r^3$  } and wherein the vitrification solution has a concentration of cryoprotectant sufficient to prevent ice formation upon contacting with solid surface (col. 4, line 1 or col. 8, lines 45-47 or col. 13, lines 14-16). The cited patent teaches the use of various biological materials including generic mammalian cells in the method for cryopreserving the biological material (col. 4, lines 54-60).

Although the cited patent is silent with regard to a particular range of thermal conductivity of the material used for a solid cryogenic surface, it clearly teaches the use of a high thermally conductive metal. According to the applicants' definitions the presently claimed range of greater than 10 W/mK is a thermal conductivity of a metal (see specification page 7, lines 6-7). Thus, the method for cryopreserving biological material of the cited patent is identical to the presently claimed method.

Therefore, the cited patent is considered to anticipate the presently claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 36-39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,780,295 [IDS-4 filed 10/09/2001, reference #2] taken with WO 99/66271 [N1].

Claims 36 and 37 as explained above. Some claims are further drawn to the use of biological material such as oocytes and/or embryos in the method for cryopreservation of biological material. Some claims are further drawn to the use of a device with stationary surface in the method for cryopreservation of biological material.

The cited patent US 5,780,295 is relied upon as explained above the disclosure of a method for cryopreservation of biological material wherein the microdroplets which have size not exceeding 10  $\mu$ L and which contain biological material suspended in solutions with cryoprotective agents, are directly contacted with a solid surface having good thermal conductivity that of a metal and a temperature of -160 °C.

The method of the patent US 5,780,295 is drawn to the use of a biological material including generic cells or generic mammalian cells but it lacks particular disclosure related to oocytes and/or embryos in the method for cryopreservation of biological material. The method of the patent US 5,780,295 is drawn to the use of a device with a rotating solid cryogenic surface

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but it lacks particular disclosure related to a device with a stationary surface in the method for cryopreservation of biological material.

The cited document WO 99/66271 is relied upon for the teaching of a method for cryopreservation of biological material by rapid freezing of biological material which occurs as result of direct contact of the biological material containing microdroplets (nebulas) with a solid surface of refrigerants (see page 20, par. 2) wherein the method is drawn to the use of biological material including oocytes (page 19, line 24) and embryos (page 22, line 5) wherein solid surface of refrigerants have good thermal conductivity including the use of metal refrigerants, for example: lead (page 10, line 5) and wherein the devices with stationary surface and/or rotating surfaces are equally or alternatively used in the method for cryopreservation of biological materials, for example: see figures 1a, 3 and/or 14. The cited WO document also teaches that cryopreservation agents are conventionally added to biological materials in order to reduce ice crystal formation and to maximize cell survival, that the optimal concentrations of cryopreservation agents significantly increase cellular survival (page 4, lines 10-15).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use various devices with either rotating or stationary cryogenic surfaces in the US 5,780,295 method for cryopreservation of biological materials including oocytes and/or embryos as suggested by WO 99/66271 with a reasonably expectation of success in cryopreserving and collecting the biological materials including oocytes and embryos because biological materials including oocytes and/or embryos can be cryopreserved by rapid freezing on direct contact with cooled solid surface as taught by WO 99/66271 and because both devices are either equivalents or equal alternatives as adequately demonstrated by WO

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99/66271. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40 and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,780,295 [IDS filed 10/09/2001, reference #2].

Claims are directed to a method for vitrification of biological material wherein the method comprises step of suspending the biological material in a cryoprotective equilibration solution having a concentration of cryoprotectant sufficient to inhibit ice formation, step of rinsing the equilibrated biological material in a vitrification solution having a concentration of cryoprotectant sufficient to prevent ice formation and step of directly contacting droplets of the vitrification solution containing biological material with a solid surface wherein the surface has a thermal conductivity greater than 10 W/mK and a temperature of about - 150°C to about -180°C, wherein the droplets have size of not exceeding 10 µL. Some claims are further drawn to the use of biological material such as cells in the method for cryopreserving the biological material.



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The cited US 5,780,295 discloses a method preservation or for vitrification of biological material such as cells or erythrocytes (example 4 see it. 1b, 2 and 3) wherein the method comprises step of suspending the biological material a cryoprotective equilibration solution with a cryoprotectant such as glycerol to obtained the equilibrated biological material (col. 21, lines 43-46), step of rinsing the equilibrated biological material in a vitrification solution with a cryoprotectant such as dextran (col. 21, lines 47-50) and step of rapidly freezing by directly contacting the nebulized solutions or droplets the vitrification solution containing biological material with a solid cryogenic surface described in this patent (col. 21, lines 60-62). The solid surface has a thermal conductivity that of a metal (col. 7, line 8) which is greater than 10 W/mK according to the applicants' definitions (specification page 7, lines 5-8). The solid surface has a temperature of about - 160°C (col. 21, line 64 and col. 4, line 23). The droplets have diameter 25-200  $\mu\text{m}$  (col. 6, lines 33) which is the size not exceeding 10  $\mu\text{L}$ , for example: volume of a droplet with diameter of 25  $\mu\text{m}$  or radius (  $r$  ) of 12.5  $\mu\text{m}$  would be  $8.2 \times 10^{-6} \mu\text{L}$  according to the formula  $v = 4/3 \pi r^3$ . The concentrations of cryoprotectants in the solutions are considered to be identical to those are claimed because the cited particular example does not report any problems related to ice formation and the teaching of the cited patent as the whole encompasses the use of cryoprotectant agents at concentrations sufficient to inhibit and/or prevent ice formation upon cooling and/or contacting with solid surface (col. 4, line 1 or col. 8, lines 45-47 or col. 11, lines 66-67). Thus, the method for cryopreserving biological material of the cited patent is identical to the presently claimed method because it comprises identical active steps and identical structural elements as required by the claimed method and/or within the meaning of the claims.

Therefore, the cited patent is considered to anticipate the presently claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 40-43 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,780,295 [IDS-4 filed 10/09/2001, reference #2] taken with WO 99/66271, Yang et al. [IDS-5, filed 12/06/2001, reference # 21], Papis et al. [IDS-5, reference #22] and Martino et al. [IDS-5, reference # 11].

Claims 40 and 41 as explained above. Some claims are further drawn to the use of biological material such as cells in the method for cryopreserving the biological material. Some claims are further drawn to the use of a device with stationary surface in the method for cryopreservation and/or vitrification of biological material.

The cited patent US 5,780,295 is relied upon as explained above the disclosure of a method for cryopreservation and/or vitrification of biological material wherein the microdroplets which have size not exceeding 10  $\mu$ L and which contain biological material suspended in vitrification solution with cryoprotective agents, are directly contacted with a solid surface having good thermal conductivity that of a metal and a temperature of -160 °C.

The method of the patent US 5,780,295 is drawn to the use of a biological material including generic cells or generic mammalian cells but it lacks particular disclosure related to oocytes and/or embryos in the method for cryopreservation and/or vitrification of biological material. The method of the patent US 5,780,295 is drawn to the use of a device with a rotating

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solid cryogenic surface but it lacks particular disclosure related to a device with a stationary surface in the method for cryopreservation and/or vitrification of biological material. The method of the patent US 5,780,295 is drawn to cryopreservation and/or vitrification of generic biological cells by using solutions with various components and various concentrations but it is silent with regard to the use of equilibration and vitrification solutions including solutions intended for cryopreservation and/or vitrification of oocytes and/or embryos. However, the cited patent US 5,780,295 clearly teaches that the type and amount of a protectant or a cryoprotective agent can be varied or modified and that the type and the amount of cryoprotective agents are determined by particular material being preserved and its intended end use (col.5, lines 33-36).

The cited document WO 99/66271 is relied upon for the teaching of a method for cryopreservation of biological material by rapid freezing of biological material which occurs as result of contacting the biological material containing microdroplets (nebulas) with a solid surface of refrigerants (see page 20, par. 2) wherein the method is drawn to the use of biological material including oocytes (page 19, line 24) and embryos (page 22, line 5) wherein solid surface of refrigerants have good thermal conductivity including the use of metal, for example: lead (page 10, line 5) and wherein the devices with stationary surface and/or rotating surfaces are equally or alternatively used in the method for cryopreservation of biological materials, for example: see figures 1, 3 and/or 14. The cited WO document also teaches that cryopreservation agents are conventionally added to biological materials in order to reduce ice crystal formation and to maximize cell survival, that the optimal concentrations of cryopreservation agents significantly increase cellular survival (page 4, lines 10-15) and that optimization protocols

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require complex cell preparations including changing concentrations of cryopreservation agents and the use of multiple steps (page 4, lines 19-21).

Further, the references by Yang et al. and Papis et al. are relied upon to demonstrate that the optimization protocols for cryopreservation and/or vitrification of mammalian oocytes and embryos require multiple steps of changing concentrations of cryopreservation agents in the equilibration solutions and in the vitrification solutions, for example: see the reference by Yang et al. at page 178, par. 2 and see the reference by Papis et al. at page 173, par. 2). Although the methods of the references by Yang et al. and by Papis et al. are drawn to the use of materials/devices such as plastic straws rather than materials/devices made from metals with good thermal conductivity, the additional reference by Martino et al. clearly demonstrates that the use of metal grids (cooper grids) are better for maximizing survival of oocytes and/or embryos than the plastic straws in the method for cryopreservation and vitrification of biological materials such as oocytes and embryos.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to use various devices with either rotating or stationary cryogenic surfaces in the US 5,780,295 method for cryopreservation and/or vitrification of biological materials as suggested by WO 99/66271 with a reasonably expectation of success in cryopreserving and collecting the biological materials including oocytes and embryos because both devices are either equivalents or equal alternatives as adequately demonstrated by WO 99/66271. It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify concentrations of cryoprotective agents in various cryoprotective solutions including equilibration and vitrification solutions in the method of US

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5,780,295 accordingly to the particular material being preserved as recommended by both US 5,780,295 and WO 99/66271 for the expected benefits in optimizing protocols for cryopreserving and/or vitrifying biological materials, including oocytes and embryos, and for maximizing survival rates of biological materials including oocytes and embryos as suggested by WO 99/66271. One of skill in the art would have been motivated to use the specific concentrations of cryoprotective agents in various equilibration and/or vitrification solutions as taught by the references by Martino et al., Yang et al. and Papis et al. accordingly to the preservation requirements as related to the specific biological materials including embryos and oocytes because the optimal protocols require changing of cryoprotective solutions as taught by WO 99/66271 and the specific concentrations ranges are within the purview of one of ordinary skill in the art of cryopreservation and vitrification of specific biological materials as demonstrated by the references by Martino et al., Yang et al. and Papis et al. One of skill in the art would have been motivated to use devices made from materials having a good thermal conductivity that of metal, for example, because the survival of biological materials on metal devices/grids are better than onto/into plastic devices as adequately proved by experiments demonstrated in the reference by Martino et al. Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented by the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

***Response to Arguments***

Applicants' arguments filed 6/27/2003 have been fully considered but they are not persuasive.

With regard to the cited patent US 5,780,295 applicants appear to argue that it does not disclose "nebulizers" delivering biological material in microdroplets of 10  $\mu$ L or less (response page 6, par. 2). Upon review of the patent it is not found true. For example: US '295 discloses "nebulizing" step "nebulizers", for example: see col. 4, line 17 or see col. 6, line 32. Moreover, the claimed invention is not limited to any specific device or "nebulizers" as it appears to be argued.

With regard to the cited patent US 5,780,295 applicants also appear to argue that it does not teach the use of concentration of cryoprotectant sufficient to inhibit and/or to prevent ice formation because it appears to state that ice crystal formation occurs during contact process (see response page 7, par. 2). However, the statement that is argued (col. 13, lines 60-66) is drawn to the description of different types of ice crystals including damaging and non-damaging ice crystals (cubic, hexagonal and amorphous) and that the goal is to achieve a non-damaging distribution of various types of ice crystals by rapid cooling or freezing. The preferred embodiments of the cited patent also teach incorporation of cryoprotective agents in amounts sufficient to prevent damaging effect of possible ice formation (for example: see col. 11, line 67 or see col.13, line 15) and, thus, the cited patent is considered to teach the use of concentration of cryoprotectants sufficient to inhibit and/or to prevent ice formation within the meaning of the claims.

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With regard to the reference by Martino et al., Yang et al. and Papis et al applicants appear to argue that the solid surface devices in the methods of the cited references are not precooled. However, the teaching of these references is relied upon for to demonstrate that the teaching about types and/or amounts of cryoprotective agents and various equilibration and vitrification solutions which are beneficial for minimizing damaging effects of freezing protocols on specific biological materials such as oocytes and/or embryos is known in the prior art. The idea to modify the optimization protocols with regard to particular biological material being preserved are suggested by US 5,780,295 and WO 99/66271 which teach method of rapid cooling of biological materials upon direct contact with precooled solid surface devices.

Applicants' arguments drawn to unexpected results (response page 7, last par.) have been fully considered but they are not found persuasive. The disclosure which is relied upon by applicants for comparative results (specification page 14, lines 12-21) refers to the IDS references that describe cryopreservation of biological material in plastic straws. The presently claimed invention is drawn to the use of devices with good thermal conductivity that of a metal. However, it has been known in the prior art that the survival of biological materials on metal devices is better than onto/into plastic devices as adequately demonstrated by the cited reference by Martino et al. (page 1063, col.1, par. 4).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (703) 308-9351. The examiner can normally be reached on Monday to Friday from 9:00 to 5:30.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn, can be reached on (703) 308-4743. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vera Afremova

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September 3, 2003

VERA AFREMOVA

PATENT EXAMINER

A handwritten signature in cursive script, reading "V. Afremova", followed by a horizontal line.